Docket No.: H1890.0537
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:

Gary D. Hodgen et al.

Application No.: 08/462,703 | Confirmation No.: 7915

Filed: June 5, 1995 | Art Unit: 1617

For: ANTIPROGESTIN METHOD FOR REDUCING SIDE EFFECTS ASSOCIATED WITH LOW DOSAGE HRT AND ORAL CONTRACEPTION AND REGULATING MENSES | Examiner: E. J. Webman

APPEAL BRIEF

MS Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

As required under § 41.37(a), this brief is filed within two months of the Notice of Appeal filed in this case on October 3, 2007, and is in furtherance of said Notice of Appeal.

The fees required under § 41.20(b)(2) are dealt with in a separate electronic filing.

This brief contains items under the following headings as required by 37 C.F.R. § 41.37 and M.P.E.P. § 1205.2:

I. REAL PARTY IN INTEREST

The real party in interest for this appeal is:

Eastern Virginia Medical School

II. RELATED APPEALS AND INTERFERENCES

There are no other appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in this appeal.

III. STATUS OF CLAIMS

A. Total Number of Claims in Application

There are 69 claims pending in application.

B. Current Status of Claims

1. Claims canceled: 1-41, 44-55, 77-81, 84, 85, 106, 107, 109, 111, and 118
2. Claims withdrawn from consideration but not canceled: 0
3. Claims pending: 42, 43, 56-76, 82, 83, 86-105, 108, 110, 112-117, and 119-134
4. Claims allowed: None
5. Claims rejected: 42, 43, 56-76, 82, 83, 86-105, 108, 110, 112-117, and 119-134

C. Claims On Appeal

The claims on appeal are claims 42, 43, 56-76, 82, 83, 86-105, 108, 110, 112-117, and 119-134

IV. STATUS OF AMENDMENTS

Applicants filed an Amendment After Final Rejection [to make minor changes (insertion of two commas) suggested by the Examiner] but it was refused entry.

V. SUMMARY OF CLAIMED SUBJECT MATTER

Because of the known adverse side-effects associated with long term administration of estrogen/progestin combination products, especially in women who smoke in the 40-44 age group, interest in achieving effective results at lower estrogen doses developed. There was a steady downward adjustment of the daily estrogen dosage, both for oral contraceptive purposes in premenopausal female and for estrogen replacement therapy in postmenopausal females during the 30+ year history of combined estrogen/progestin oral contraception preceding the present invention. As a result, the more recent oral products are much safer with regard to the incidence and severity of estrogen-linked clotting disorders, as well as the cumulative impact of more "lipid friendly" progestins that maintain high density lipoprotein cholesterol levels in circulation.

Two principal issues are involved when considering lowering the daily dose of estrogen-progestin medications even lower, viz., (1) maintenance of efficacy; and (2) avoidance of further erosion in the control of endometrial bleeding. Even the lowest dose oral contraceptive products available as of the priority date of this application in 1992 which demonstrated sustained efficacy, still manifested an overall increase in the incidence of bleeding control problems, both in the form of breakthrough bleeding (untimely flow or spotting) or withdrawal amenorrhea during the "pill free" week (expected menses), as estrogen/progestin doses were reduced.

The present invention is based on the discovery that the bleeding control problems could be reduced by the use of an antiprogestin as described in the application.

A designation of exemplary support in the application for each independent claim on appeal is as follows:

42. A method of hormone replacement therapy (page 3, lines 23-26), comprising administering to a woman in need thereof an effective amount of estrogen in combination with an effective amount of a progestin (page 4, lines 29-30; page 7, lines 25-28), and an amount of antiprogestin (page 4, line 21; page 9, line 31 et seq.) effective to ameliorate uterine bleeding problems associated with hormone replacement therapy (page 3, lines 23-26; page 7, lines 3-7).

56. A method of hormone replacement therapy (page 3, lines 23-26) comprising administering to a woman in need thereof an effective amount of estrogen, with progestin administration (page 4, lines 29-30; page 7, lines 25-28), and an amount of antiprogestin effective to inhibit breakthrough bleeding (page 3, lines 20-26).

61. A method of hormone replacement therapy (page 3, lines 23-26) comprising administering to a woman in need thereof an effective amount of estrogen, with progestin administration (page 4, lines 29-30; page 7, lines 25-28), and an amount of antiprogestin equivalent to an oral dose of about 1.0 to about 10 mg/kg of weight of the woman (page 11, lines 19-22).

67. A method of hormone replacement therapy (page 3, lines 23-26) comprising administering to a woman in need thereof an effective amount of estrogen, with progestin administration (page 4, lines 29-30; page 7, lines 25-28), and an antimitotically effective amount of antiprogestin (page 22, lines 30-33).

72. A method of hormone replacement therapy (page 3, lines 23-26) comprising administering to a woman in need thereof an effective amount of estrogen, with progestin

administration (page 4, lines 29-30; page 7, lines 25-28), and an amount of antiprogestin effective to inhibit endometrial growth (page 22, lines 30-36).

82. A method of avoiding the bleeding problems associated with administering to a female mammal dosage amounts of an estrogen low enough to create incidents of breakthrough bleeding and withdrawal amenorrhea during hormone replacement therapy (page 3, lines 9-26), which comprises (a) administering the estrogen daily without interruption (page 9, lines 18-19) and (b) administering progestin (page 9, lines 18-19) and (c) periodically, at intervals of at least about a month (page 6, lines 17-19, page 7, lines 3-5), administering to the female an amount of an antiprogestin effective to reduce or eliminate breakthrough bleeding (page 3, lines 9-26) and, optionally, to induce sloughing of accumulated endometrial tissue and thereby induce menses (page 9, lines 29-30).

102. A kit containing at least about 20 estrogen and progestin-containing tablets (page 10, lines 30-36; page 11, line 12), which collectively contain amounts thereof which are too low to avoid breakthrough bleeding incidents where administration of the tablets is interrupted for a week during each monthly cycle to induce menses (page 10, lines 30-36); and containing a tablet, arranged in the kit so as to be taken after at least 20 of the estrogen and progestin-containing tablets have been taken, which contains an amount of antiprogestin effective to induce menses (page 10, line 30 to page 11, line 3). (See also, page 24, line 12 et seq.)

108. A method of avoiding the bleeding problems associated with administering to a female mammal dosage amounts of an estrogen low enough to create incidents of breakthrough bleeding and withdrawal amenorrhea during hormone replacement therapy

(page 3, lines 9-26), which comprises (a) administering the estrogen daily without interruption (page 9, lines 18-19) and (b) administering progestin (page 9, lines 18-19) and (c) periodically, at intervals of at least about a month (page 6, lines 17-19, page 7, lines 3-5), administering to the female an amount of an antiprogestin effective to reduce or eliminate breakthrough bleeding (page 3, lines 9-26) and, optionally, to induce sloughing of accumulated endometrial tissue whereby menses is induced (page 9, lines 29-30).

128. A kit containing estrogen and progestin-containing tablets (page 10, lines 30-36; page 11, line 12), which collectively when 21 thereof are taken on successive days by a female human being contain amounts thereof which are too low to avoid breakthrough bleeding incidents where administration of the tablets is interrupted for a week during each monthly cycle to induce menses (page 10, lines 30-36); and containing a tablet, arranged in a kit so as to be taken after at least 20 of the estrogen and progestin-containing tablets have been taken, which contains an amount of an antiprogestin effective to induce menses (page 10, line 30 to page 11, line 3). (See also, page 24, line 12 et seq.)

132. A pharmaceutical composition in solid oral unit dosage form (page 4a, lines 7-12; page 9, lines 11) comprising amounts of an estrogen and of a progestin equivalent to 5 mcg. to 35 mcg. of ethinyl estradiol and 0.5 mg. to 1.5 mg. of norethindiol acetate, respectfully (page 7, lines 29-30), and an amount of an antiprogestin effective to induce menses in a female human being who has ingested daily for at least 20 days corresponding amounts of the estrogen and progestin (page 10, line 30 to page 11, line 3). (See also, page 24, line 12 et seq., and original claim 25).

For all dependent claims argued separately, one or more of the foregoing independent claims contains the same feature and sets forth exemplary support in the application for those claims.

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

All claims stand rejected on the grounds of non-statutory obvious-type double patenting rejection over claims 1-20 of Hodgen US 5,468,736.

VII. ARGUMENT

The known adverse side-effects associated with long term administration of estrogen/progestin combination medications lead to a steady downward adjustment of the daily estrogen dosage, both for oral contraceptive purposes in premenopausal female and for estrogen replacement therapy in postmenopausal females during the 30+ year history of combined estrogen/progestin oral medications preceding the present invention. As a result, the newer oral formulations were much safer with regard to the incidence and severity of estrogen-linked clotting disorders, as well as the cumulative impact of more "lipid friendly" progestins that maintain high density lipoprotein cholesterol levels in circulation.

Two principal issues are involved when considering lowering the daily dose of estrogen-progestin medications even lower, viz., (1) maintenance of efficacy; and (2) avoidance of further erosion in the control of endometrial bleeding. Even the lowest dose

oral products available as of the priority date of this application in 1992 which demonstrated sustained efficacy, still manifested an overall increase in the incidence of bleeding control problems, both in the form of breakthrough bleeding (untimely flow or spotting) or withdrawal amenorrhea during the "pill free" week (expected menses), as estrogen/progestin doses were reduced.

The present invention is based on the discovery that the bleeding control problems could be reduced by the use of an antiprogestin. The claims on appeal recite the method of using the estrogen-progestin-antiprogestin in various iterations, and kits for use in those methods. Corresponding patents have issued in numerous countries. The applicants have been seeking a United States patent on this invention since 1992.

The sole rejection in this case is on the grounds of obviousness type double patenting over a patent issued to one of the coinventors in this application which, until about one year ago, was owned by an unrelated entity. The issued patent is US 5,468,736 (hereinafter the "'736 patent"). Although this type of rejection becomes moot if a terminal disclaimer is filed, the filing of such a disclaimer did not even become a possibility until title was acquired by the current assignee. Since then, it has been determined not to submit a terminal disclaimer because not only are the claims on appeal not obvious over the '736 patent, but avoiding the issue by means of a disclaimer would, after 15 years of application pendency, result in a loss of more than 70% of the patent term to which this case would be entitled.

The '736 patent contains 12 method claims, each of which is for a method of hormone replacement therapy (HRT) employing estrogen and antiprogestin "in the absence of progestin". There are also 8 kit claims which recite the presence of estrogen and

antiprogestin without any indication of progestin being present. All claims of the patent also require the antiprogestin to be present in an amount sufficient to effect a state of substantial amenorrhea, i.e., the absence or cessation of menstrual periods.

One major difference between the claims on appeal and the '736 patent is that the claims on appeal require the presence of progestin and all claims of the '736 patent require its absence. This difference permeates all claims on appeal but there further differences in individual claims such that additional consideration is necessary. As a result, all claims do not stand and fall together. There are subsets of the appealed claims which have additional features further making them unobvious.

ALL CLAIMS ARE UNOBVIOUS

All of the claims on appeal require the presence of progestin while all claims of the '736 patent explicitly require its absence. Adding progestin to the '736 patent claims would violate an explicit requirement of those claims and destroy the very basis on which those claims are predicated. That is not only illogical, but it is also impermissible. *Ex parte Hartmann*, 186 USPQ 366 (BPAI 1974).

Preparatory to an argument that the presence of progestin is obvious, the Final Rejection avers the '736 patent "stipulates that endometrial carcinoma is decreased with progestin (column 2, lines 15-16)", and in an attempt to excuse reliance material from the patent outside its claims, which is not permitted in a double patenting rejection, an Advisory Action asserts this teaching is found in a background section. That attempted justification is invalid since not only do those lines appear in the middle of a paragraph transitioning between the prior art and the invention but also, it takes a phrase out of

context in that the sentence states that progestins cause "unwanted vaginal bleeding that markedly reduces therapy compliance among postmenopausal women." In other words, the disclosure on which reliance is attempted, in context, actually reinforces the essential requirement of the '736 patent's requirement that there be an "absence of progestin".

In an effort to establish obviousness and improperly relying on more that the '736 patent claims, an Advisory Action avers that "the absence of progestin to achieve the claimed property is not a prohibition against adding an additional active to achieve an additional benefit." Whatever validity this assertion may have as to actives other than progestin, it cannot be applied to progestin. If, as hypothesized in the quoted assertion, the absence of progestin is required to achieve the claimed property, then adding progestin would prevent achieving the "claimed" (desired) property and that simply makes no sense whatsoever.

Still further, the '736 patent claims employ antiprogestin. Adding a material which has the opposite activity (progestin) facially suggests the activity of the antiprogestin would be neutralized. That also make no sense.

The claims on appeal which require the presence of progestin are unobvious over the '736 patent claims which require progestin to be absent.

THE BLEEDING CLAIMS ARE NOT OBVIOUS

All claims of the '736 patent require the antiprogestin to be present in an amount sufficient to effect a state of substantial amenorrhea, i.e., to prevent vaginal bleeding caused by the estrogen in the absence of progestin. As noted earlier, progestin also causes vaginal bleeding. The Examiner to date has not proposed any reason why it is obvious

that the amount of antiprogestin should be that sufficient to combat bleeding induced by an agent which is explicitly excluded by the '736 patent claims.

The appealed claims of this subset are 42-44, 56-60, 82-105 and 132-134.

THE MENSES CLAIMS ARE UNOBVIOUS

Another subset of appealed claims more specifically references menses as opposed to vaginal bleeding in general. These are claims 82, 102-105 and 132-134. All claims of the '736 patent require the antiprogestin to be present in an amount sufficient to effect a state of substantial amenorrhea, i.e., to realize an absence or cessation of menstrual periods. The Examiner has not proposed any reason that this subset of claims, which call for the antiprogestin amount to do the opposite and cause or permit menstrual periods, would be obvious. There is no basis for the double patenting rejection of this subset of claims.

THE "PERIODIC" CLAIMS ARE NOT OBVIOUS

Another group of appealed claims which requires separate consideration are those which specify the administration of the antiprogestin is periodic. This group includes claims 43, 57, 59, 62, 64, 68, 70, 73, 75, 82-105, and 108-131.

Claims 2, 4 and 6 of the '736 patent call for daily antiprogestin administration, and claim 8 calls for depot administration (a form of continuous administration). The administration on a periodic basis, of once a month or longer periods, as in this group, is clearly unobvious. The PTO has not proposed any reason why such periodic administration would be obvious.

CONCLUSION

The entire set of appealed claims, as well as several subsets of them, are not obvious over the claims of the '736 patent. The obviousness-type double patenting rejection is not tenable and should be reversed.

VIII. CLAIMS

A copy of the claims involved in the present appeal is attached hereto as Appendix A.

Dated: December 3, 2007

Respectfully submitted,

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APPENDIX A

Claims Involved in the Appeal of Application Serial No. 08/462,703

42. A method of hormone replacement therapy, comprising administering to a woman in need thereof an effective amount of estrogen in combination with an effective amount of a progestin, and an amount of antiprogestin effective to ameliorate uterine bleeding problems associated with hormone replacement therapy.

43. A method of claim 42, wherein the antiprogestin is administered periodically.

44. A method of claim 42, wherein the antiprogestin is administered continuously.

56. A method of hormone replacement therapy comprising administering to a woman in need thereof an effective amount of estrogen, with progestin administration, and an amount of antiprogestin effective to inhibit breakthrough bleeding.

57. A method of claim 56 wherein the antiprogestin is administered periodically.

58. A method of claim 56, wherein the antiprogestin is administered continuously.

59. A method of claim 57, wherein the estrogen is administered continuously.

60. A method of claim 58, wherein the estrogen is administered continuously.

61. A method of hormone replacement therapy comprising administering to a woman in need thereof an effective amount of estrogen, with progestin administration, and an amount of antiprogestin equivalent to an oral dose of about 1.0 to about 10 mg/kg of weight of the woman.

62. A method of claim 61, wherein the antiprogestin is administered periodically.

63. A method of claim 61, wherein the antiprogestin is administered continuously.

64. A method of claim 62, wherein the estrogen is administered continuously.

65. A method of claim 63, wherein the estrogen is administered continuously.

66. A method of claim 61, wherein the dose is 50-500 mg.

67. A method of hormone replacement therapy comprising administering to a woman in need thereof an effective amount of estrogen, with progestin administration, and an antimitotically effective amount of antiprogestin.

68. A method of claim 67 wherein the antiprogestin is administered periodically.

69. A method of claim 67, wherein the antiprogestin is administered continuously.

70. A method of claim 68, wherein the estrogen is administered continuously.

71. A method of claim 69, wherein the estrogen is administered continuously.

72. A method of hormone replacement therapy comprising administering to a woman in need thereof an effective amount of estrogen, with progestin administration, and an amount of antiprogestin effective to inhibit endometrial growth.

73. A method of claim 72, wherein the antiprogestin is administered periodically.

74. A method of claim 72, wherein the antiprogestin is administered continuously.

75. A method of claim 73, wherein the estrogen is administered continuously.

76. A method of claim 74, wherein the estrogen is administered continuously.

82. A method of avoiding the bleeding problems associated with administering to a female mammal dosage amounts of an estrogen low enough to create incidents of breakthrough bleeding and withdrawal amenorrhea during hormone replacement therapy, which comprises (a) administering the estrogen daily without interruption and (b) administering progestin and (c) periodically, at intervals of at least about a month, administering to the female an amount of an antiprogestin effective to reduce or eliminate breakthrough bleeding and, optionally, to induce sloughing of accumulated endometrial tissue and thereby induce menses.

83. A method of claim 82, wherein the estrogen and the daily dose thereof is ethinyl estradiol or an ester thereof in the amount of 5-15 mcg/day, mestranol in the amount of 20-25 mcg/day or conjugated estrogens in the amount of 5-15 mcg/day.

86. A method of claim 82, wherein the amounts of the estrogen and the progestin which are administered are effective to suppress endometrial proliferation.

87. A method of claim 82, wherein the administration of the progestin is continued uninterrupted throughout the cycle.

88. A method of claim 82, wherein the administration of progestin is interrupted proximate the day of antiprogestin administration.

89. A method of claim 82, wherein the antiprogestin is administered about monthly.

90. A method of claim 82, wherein the antiprogestin is administered orally.

91. A method of claim 82, wherein the antiprogestin is onapristone or mifepristone.

92. The method of claim 82, wherein the progestin is gestodene or norethindrone acetate.

93. The method of claim 82, wherein the estrogen, the progestin and the antiprogestin are administered orally; wherein the administration of the progestin and the estrogen is continued uninterrupted throughout the cycle and wherein the estrogen and the daily dose thereof is ethinyl estradiol or estradiol or an ester thereof in the amount of 5-15 mcg/day, mestranol in the amount of 20-25 mcg/day or conjugated estrogens in the amount of 5-15 mcg/day.

94. The method of claim 82, wherein the female is a para- or postmenopausal woman.

95. The method of claim 94, wherein the estrogen is administered in combination with a progestin.

96. The method of claim 95, wherein the administration of the progestin is continued uninterrupted during the period of antiprogestin administration.

97. The method of claim 95, wherein the administration of the progestin is interrupted proximate the period of antiprogestin administration.

98. The method of claim 94, wherein the antiprogestin is onapristone or mifepristone.

99. The method of claim 94, wherein the estrogen and the daily dose thereof is ethinyl estradiol or estradiol or an ester thereof in the amount of 5-15 mcg/day, mestranol in the amount of 20-25 mcg/day or conjugated estrogens in the amount of 5-15 mcg/day.

100. The method of claim 95, wherein the antiprogestin is onapristone or mifepristone; and wherein the progestin is gestodene or norethindrone acetate.

101. The method of claim 95, wherein the estrogen, progestin and antiprogestin are administered orally; wherein the antiprogestin is administered at longer than one month intervals; wherein the administration of the progestin is continued uninterrupted during the period of antiprogestin administration; and wherein the estrogen and the daily dose thereof is ethinyl estradiol or estradiol or an ester thereof in the amount of 5-15 mcg/day, mestranol in the amount of 20-25 mcg/day or conjugated estrogens in the amount of 5-15 mcg/day.

102. A kit containing at least about 20 estrogen and progestin-containing tablets, which collectively contain amounts thereof which are too low to avoid breakthrough bleeding incidents where administration of the tablets is interrupted for a week during each monthly cycle to induce menses; and containing a tablet, arranged in the kit so as to be taken after at least 20 of the estrogen and progestin-containing tablets have been taken, which contains an amount of antiprogestin effective to induce menses.

103. A kit according to claim 102, containing 28 of the estrogen and progestin-containing tablets, arranged to be taken sequentially with the antiprogestin-containing tablet positioned as the 20th or later tablet in the sequence.

104. A kit according to claim 102, wherein the antiprogestin is onapristone or mifepristone; and wherein the progestin is gestodene or norethindrone acetate.

105. A kit according to claim 102, wherein the estrogen and the daily dose thereof is ethinyl estradiol or estradiol or an ester thereof in the amount of 5-15 mcg/day, mestranol in the amount of 20-25 mcg/day or conjugated estrogens in the amount of 5-15 mcg/day.

108. A method of avoiding the bleeding problems associated with administering to a female mammal dosage amounts of an estrogen low enough to create incidents of breakthrough bleeding and withdrawal amenorrhea during hormone replacement therapy, which comprises (a) administering the estrogen daily without interruption and (b) administering progestin and (c) periodically, at intervals of at least about a month, administering to the female an amount of an antiprogestin effective to reduce or eliminate breakthrough bleeding and, optionally, to induce sloughing of accumulated endometrial tissue whereby menses is induced.

110. The method of claim 108, wherein the estrogen is administered in combination with a progestin in an amount effect to suppress endometrial proliferation.

112. The method of claim 108, wherein the administration of the progestin and estrogen is interrupted proximate the day of antiprogestin administration.

113. The method of claim 108, wherein the antiprogestin is administered about monthly.

114. The method of claim 108, wherein the antiprogestin is administered orally.

115. The method of claim 108, wherein the antiprogestin is mifepristone.

116. The method of claim 108, wherein the estrogen is ethinyl estradiol.

117. The method of claim 108, wherein the progestin is norethindrone acetate.

119. The method of claim 108, wherein the female is a para- or postmenopausal woman.

120. The method of claim 119, wherein the antiprogestin is administered at longer than monthly intervals.

121. The method of claim 108, wherein the administration of the progestin and estrogen is continued uninterrupted throughout the cycle, including during menses.

122. The method of claim 121, wherein the administration of the progestin is interrupted proximate the day of the antiprogestin administration.

123. The method of claim 119, wherein the antiprogestin is administered orally.

124. The method of claim 119, wherein the antiprogestin is mifepristone.

125. The method of claim 119, wherein the estrogen is ethinyl estradiol or estradiol.

126. The method of claim 108, wherein the progestin is norethindrone acetate.

127. The method of claim 108, wherein the female mammal is a para- or postmenopausal woman, wherein the antiprogestin is administered orally at longer than one month intervals and the administration of the progestin and estrogen is continued uninterrupted during the period of antiprogestin administration.

128. A kit containing estrogen and progestin-containing tablets, which collectively when 21 thereof are taken on successive days by a female human being contain amounts thereof which are too low to avoid breakthrough bleeding incidents where administration of the tablets is interrupted for a week during each monthly cycle to induce menses; and containing a tablet, arranged in a kit so as to be taken after at least 20 of the estrogen and progestin-containing tablets have been taken, which contains an amount of an antiprogestin effective to induce menses.

129. A kit according to claim 128, containing 28 of the estrogen and progestin containing tablets, arranged to be taken sequentially with the anti-progestin containing tablet positioned as the 20^{th} or later tablet in the sequence.

130. A kit according to claim 128, wherein the estrogen is ethinyl estradiol, the progestin is norethindrone acetate and the antiprogestin is mifepristone.

131. A kit according to claim 128, wherein the estrogen is ethinyl estradiol, the progestin is gestodene and the antiprogestin is onapristone.

132. A pharmaceutical composition in solid oral unit dosage form comprising amounts of an estrogen and of a progestin equivalent to 5 mcg. to 35 mcg. of ethinyl estradiol and 0.5 mg. to 1.5 mg. of norethindiol acetate, respectfully, and an amount of an antiprogestin effective to induce menses in a female human being who has ingested daily for at least 20 days corresponding amounts of the estrogen and progestin.

133. A pharmaceutical composition according to claim 132, containing 0.5 to 35 mcg. ethinyl estradiol, 0.5 to 35 mg norethindrone acetate and 50 to 500 mg. of mifepristone.

134. A pharmaceutical composition according to claim 132, containing 0.5 to 35 mcg. ethinyl estradiol, 10 to 15 mcg. gestodene and 50 to 500 mg. of onapristone.

APPENDIX B

No evidence pursuant to §§ 1.130, 1.131, or 1.132 or entered by or relied upon by the examiner is being submitted.

APPENDIX C

No related proceedings are referenced in II. above, hence copies of decisions in related proceedings are not provided.